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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/857,518	12/12/2001	Asaph Aharoni	4916US	5379

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EXAMINER

SAIDHA, TEKCHAND

ART UNIT PAPER NUMBER

1652

DATE MAILED: 08/22/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Advisory Action Before the Filing of an Appeal Brief	Application No. 09/857,518	Applicant(s) AHARONI ET AL.	
	Examiner Tekchand Saidha	Art Unit 1652	

--The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

THE REPLY FILED 27 July 2005 FAILS TO PLACE THIS APPLICATION IN CONDITION FOR ALLOWANCE.

1. ☒ The reply was filed after a final rejection, but prior to or on the same day as filing a Notice of Appeal. To avoid abandonment of this application, applicant must timely file one of the following replies: (1) an amendment, affidavit, or other evidence, which places the application in condition for allowance; (2) a Notice of Appeal (with appeal fee) in compliance with 37 CFR 41.31; or (3) a Request for Continued Examination (RCE) in compliance with 37 CFR 1.114. The reply must be filed within one of the following time periods:

- a) ☒ The period for reply expires 6 months from the mailing date of the final rejection.
b) ☐ The period for reply expires on: (1) the mailing date of this Advisory Action, or (2) the date set forth in the final rejection, whichever is later. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of the final rejection.

Examiner Note: If box 1 is checked, check either box (a) or (b). ONLY CHECK BOX (b) WHEN THE FIRST REPLY WAS FILED WITHIN TWO MONTHS OF THE FINAL REJECTION. See MPEP 706.07(f).

Extensions of time may be obtained under 37 CFR 1.136(a). The date on which the petition under 37 CFR 1.136(a) and the appropriate extension fee have been filed is the date for purposes of determining the period of extension and the corresponding amount of the fee. The appropriate extension fee under 37 CFR 1.17(a) is calculated from: (1) the expiration date of the shortened statutory period for reply originally set in the final Office action; or (2) as set forth in (b) above, if checked. Any reply received by the Office later than three months after the mailing date of the final rejection, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

NOTICE OF APPEAL

2. ☒ The Notice of Appeal was filed on 27 July 2005. A brief in compliance with 37 CFR 41.37 must be filed within two months of the date of filing the Notice of Appeal (37 CFR 41.37(a)), or any extension thereof (37 CFR 41.37(e)), to avoid dismissal of the appeal. Since a Notice of Appeal has been filed, any reply must be filed within the time period set forth in 37 CFR 41.37(a).

AMENDMENTS

3. ☐ The proposed amendment(s) filed after a final rejection, but prior to the date of filing a brief, will not be entered because
(a) ☒ They raise new issues that would require further consideration and/or search (see NOTE below);
(b) ☐ They raise the issue of new matter (see NOTE below);
(c) ☐ They are not deemed to place the application in better form for appeal by materially reducing or simplifying the issues for appeal; and/or
(d) ☐ They present additional claims without canceling a corresponding number of finally rejected claims.

NOTE: Claim 47 is not entered. (See 37 CFR 1.116 and 41.33(a)).

4. ☐ The amendments are not in compliance with 37 CFR 1.121. See attached Notice of Non-Compliant Amendment (PTOL-324).
5. ☒ Applicant's reply has overcome the following rejection(s): 112 (written Description), 112 2nd and 101.
6. ☐ Newly proposed or amended claim(s) _____ would be allowable if submitted in a separate, timely filed amendment canceling the non-allowable claim(s).
7. ☐ For purposes of appeal, the proposed amendment(s): a) ☐ will not be entered, or b) ☒ will be entered and an explanation of how the new or amended claims would be rejected is provided below or appended.
The status of the claim(s) is (or will be) as follows:
Claim(s) allowed: 45 and 46.
Claim(s) objected to: _____
Claim(s) rejected: 19-21 and 43.
Claim(s) withdrawn from consideration: 1-18, 22-33, 35-40 and 47.

AFFIDAVIT OR OTHER EVIDENCE

8. ☐ The affidavit or other evidence filed after a final action, but before or on the date of filing a Notice of Appeal will not be entered because applicant failed to provide a showing of good and sufficient reasons why the affidavit or other evidence is necessary and was not earlier presented. See 37 CFR 1.116(e).
9. ☐ The affidavit or other evidence filed after the date of filing a Notice of Appeal, but prior to the date of filing a brief, will not be entered because the affidavit or other evidence failed to overcome all rejections under appeal and/or appellant fails to provide a showing of a good and sufficient reasons why it is necessary and was not earlier presented. See 37 CFR 41.33(d)(1).
10. ☐ The affidavit or other evidence is entered. An explanation of the status of the claims after entry is below or attached.

REQUEST FOR RECONSIDERATION/OTHER

11. ☒ The request for reconsideration has been considered but does NOT place the application in condition for allowance because: see Office Action for details.
12. ☐ Note the attached Information Disclosure Statement(s). (PTO/SB/08 or PTO-1449) Paper No(s). _____
13. ☐ Other: _____

Advisory Action

1. Applicants Amendment After-Final filed July 27, 2005, is entered in-part and with respect to pending claims 19-21, 43 and 45-46. Claim 47, is not entered because it raises new issues that would require further consideration and/or search.

2. Claims 19-21, 43 and 45-46 corresponding to SEQ ID Nos. 6 and 31, are pending and under consideration in this examination.

3. **Claims withdrawn** :

Claims 1-18, 22-33, 35-40 (fully) remain withdrawn from further consideration by the examiner, 37 CFR 1.142(b), as being drawn to a non-elected invention, the requirement having been traversed, at least in-part.

4. ***Priority***

Acknowledgment is made of Applicants' claim for priority based on applications filed in EPO on 12/02/1998 [98204018.0] & 03/12/1999 [99200739.3]. Certified copies of the documents have been received.

5. Any objection or rejection of record which is not expressly repeated in this Office Action has been overcome by Applicant's response and withdrawn.

6. Applicant's arguments filed as per the amendment cited above have been fully considered but they are not deemed to be persuasive. The reasons are discussed following the rejection(s).

7. ***Enablement***

Claims 19-21 & 43 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for an alcohol acyl transferase of SEQ ID NO: 6 and an alcohol dehydrogenase of SEQ ID NO: 31 (both from strawberry), does not reasonably provide enablement for any alcohol acyl transferase having 30%, 50% or 70% identity to SEQ ID NO: 6; or any alcohol dehydrogenase having 55% identity to SEQ ID NO: 31; or any fragments thereof. The specification does not enable any person skilled in the art to which

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it pertains, or with which it is most nearly connected, to make the invention commensurate in scope with these claims.

The scope of the claims is not commensurate with the enablement provided by the disclosure with regard to the extremely large number of alcohol acyl transferases and alcohol dehydrogenases broadly encompassed by the claims. Since the amino acid sequence of a protein determines its structural and functional properties, predictability of which changes can be tolerated in a protein's amino acid sequence and obtain the desired activity requires a knowledge of and guidance with regard to which amino acids in the protein's sequence, if any, are tolerant of modification and which are conserved (i.e. expectedly intolerant to modification), and detailed knowledge of the ways in which the proteins' structure relates to its function. However, in this case the disclosure is limited to the nucleotide and encoded amino acid sequences of alcohol acyl transferase and alcohol dehydrogenase of SEQ ID NO: 6 & 31 respectively.

While recombinant and mutagenesis techniques are known, it is not routine in the art to screen for multiple substitutions or multiple modifications, as encompassed by the instant claims, and the positions within a protein's sequence where amino acid modifications can be made with a reasonable expectation of success in obtaining the desired activity/utility are limited in any protein and the result of such modifications is unpredictable. In addition, one skilled in the art would expect any tolerance to modification for a given protein to diminish with each further and additional modification, e.g. multiple substitutions.

The specification does not support the broad scope of the claims which encompass all modifications of any alcohol acyl transferase with 30%, 50 or 70% identity to the enzyme of SEQ ID NO: 6, or all modifications of any alcohol dehydrogenase with 55% identity to the enzyme of SEQ ID NO: 31, because the specification does not establish: (A) regions of the protein structure which may

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be modified without effecting alcohol acyl transferase or alcohol dehydrogenase activity; (B) the general tolerance of alcohol acyl transferase or alcohol dehydrogenase to modification and extent of such tolerance; (C) a rational and predictable scheme for modifying any alcohol acyl transferase or alcohol dehydrogenase residues with an expectation of obtaining the desired biological function; and (D) the specification provides insufficient guidance as to which of the essentially infinite possible choices is likely to be successful.

Thus, applicants have not provided sufficient guidance to enable one of ordinary skill in the art to make and use the claimed invention in a manner reasonably correlated with the scope of the claims broadly including alcohol acyl transferase or alcohol dehydrogenase with an enormous number of amino acid modifications of the of SEQ ID Nos: 6 & 31. The scope of the claims must bear a reasonable correlation with the scope of enablement (In re Fisher, 166 USPQ 19 24 (CCPA 1970)). Without sufficient guidance, determination of alcohol acyl transferase or alcohol dehydrogenase having the desired biological characteristics is unpredictable and the experimentation left to those skilled in the art is unnecessarily, and improperly, extensive and undue. See In re Wands 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir, 1988).

Applicants' Arguments (old):

Applicants based upon the calculated % homology between some of the recently identified acyltransferases and SEQ ID NO: 6, argue that acyl transferases from banana, apple & melon have the same enzymatic activity and yet have less than 30% sequence homology with respect to strawberry [SEQ ID NO: 6], and are therefore enabled by the present specification.

Applicants' arguments are well taken, however, such diversity among the various fruit crops with respect to a single enzyme, further makes the job of one skilled in the art all the more difficult. Since a uniform strategy cannot be rationalized as to which amino acids or regions of the protein structure among the various species which may be modified and which may not be modified

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without effecting alcohol acyl transferase or alcohol dehydrogenase activities; and the extent of tolerance of the protein(s) to such modifications without effecting the desired enzymatic function remains highly unpredictable. The rejection is maintained for all of the above reasons and those already made of record.

Applicants' Arguments (new):

Applicants argue that at page 42, lines 16-20 of the as-filed specification, conserved sequences are set forth, which, as explained in the specification, can serve as motifs for the production of nucleotide primers for identifying related genes. Primers based on these motifs may be used to screen polynucleotide extracts from plants to locate proteins that have alcohol acyl transferase activity. One of ordinary skill in the art would be able to use the primers as mentioned in the specification for amplification reactions on cDNA extracts of plant genetic material, see, Example 3.7 beginning on page 55 of the as-filed specification, and to devise "degenerate" primers based on a consensus sequence (as was done in Example 3.7). Guidance on the determination of alcohol acyltransferase activity is provided in the as-filed specification at Examples 4.4, 4.5, and 5 (pages 59 to 65), demonstrating that the genes specified therein show such activity. Accordingly, it is requested this rejection be withdrawn and claims 19 through 21 and 43 allowed. Applicants also note that support for new claim 47 may be found in the specification at the citations set forth in this paragraph.

Applicants' new argument is considered no different than previously presented. No clear-cut guidance is provided of modifying SEQ ID NO: 6 or 31 to the tune of 30%, 50%, 55% or 70% as explained in the rejection. The rejection is therefore maintained.

Applicants' argue that support for claim 47 may be found in the specification at the citations set forth in this paragraph. This is not understood. Please cite the specific page(s) and lines. However, this is for

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future reference, since claim 47 is not under consideration in this Office Action. As indicated before (paragraph 1 of page 2 of this Office Action) Claim 47, is not entered because it raises new issues that would require further consideration and/or search.

8. Claim Rejections - 35 USC § 112 (second paragraph)

Claim 43 is rejected under 35 U.S.C. §112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 43 recite the phrase 'kit for screening ...volatile ester compounds'. The claim is indefinite because it is unclear how a kit comprising a polypeptide of SEQ ID NO: 6 or 31 or fragments thereof is sufficient in diagnosing 'volatile ester compound'. How do one measure these volatile ester compounds? Does the kit comprise instructions for testing volatile ester compounds? The rejection is maintained for these reasons.

9. Claims 45-46 are allowed.

10. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Tekchand Saidha (Ph.D.) whose telephone number is (571) 272-0940. The examiner can normally be reached on Monday-Friday from 8:15 am to 4:45 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ponnathapu Achutamurthy, can be reached at (571) 272-0928. The fax phone number for this Group in the Technology Center is 703 872-9306.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is 571 272-1600.



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